REMARKS

The claims have been amended to expedite prosecution. Claims 9-10 and 20-21 have been canceled; the limitations of claims 12, 16 and 18 have been incorporated into claims 11, 15 and 17; therefore claims 12, 16 and 18 have been canceled as redundant. Claim 19 has been amended just to correct its dependency. No new matter has been added and entry of the amendment is respectfully requested.

Formal Matters

Corrected drawings are enclosed with this response. Applicants note the criticism concerning sequence listing; no errors in the sequence information and amendment filed 17 April 2002 have been noted. Applicants respectfully request clarification of the notation at the top of page 4 of the Office action.

The Invention

The invention provides methods to introduce nucleic acids into histocultured tissue and to transplant the tissue containing the heterologous nucleic acids into intact subjects. The efficiency of doing so is improved in the case of hair follicles if the hair follicle is in anagen and in every case the uptake of nucleic acid is enhanced by treatment of the histoculture with collagenase. Applicants appreciate that these aspects of the invention appear free of the art.

The Rejections Under 35 U.S.C. § 112, First Paragraph

Claim 9 was rejected under 35 U.S.C. § 112, first paragraph, as assertedly lacking written description. While applicants strongly disagree with the application of the legal principles stated to a claim directed to a method which is basically independent of the nature of the nucleic acid to be provided the hair follicle, in order to simplify prosecution, claim 9 has simply been canceled.

As to the rejections of claims 1-21, this basis for rejection appears to reside in an asserted lack of utility rather than lack of enablement or written description. There appears to be no

rationale which asserts that nucleic acids cannot be successfully transferred to histocultured tissue or that the histocultured tissue cannot be successfully provided to an intact animal according to the methods described and claimed. Indeed, the documents cited by the Office in the context of an art rejection of certain claims, Chapelier, and Poston, verify capability of transplanting *ex vivo* modified intact tissue into whole body recipients (once the tissue has been modified). The basis for rejection appears to reside in the impression that the only utility for performing the methods claimed is in the context of gene therapy, and that gene therapy has had a troubled past and continues to have a troubled present.

But the methods of the invention are not about gene therapy. The methods of the invention are simply tools. They offer more effective ways to modify tissues in intact animals for whatever purpose. On such purpose, for example, is illustrated in Example 2 where the nucleic acids encode a protein which is simply used to label specific tissues in an experimental animal. In this context, the method of the invention amounts to a research tool. In other aspects, the methods of the invention, rather than requiring expression, may simply serve to introduce nucleic acids as *per se* pharmaceuticals. The ultimate applications to which the methods of the invention are directed are many, and all will be benefited by improvements in this aspect of each application.

Even if gene therapy were the only conceivable utility or purpose of the invention methods (which it is not), and even if gene therapy is not fully developed, this does not mean that the methods of the invention are useless or not enabled. As the Office itself points out, "the Achilles heel of gene therapy is gene delivery." This is the precise problem that the methods of the invention solve. (If the problem were already solved, what would the point of the invention?) If there are additional problems which the invention does not solve, others are entitled to claim

those. What the present inventors have contributed is an enhanced method of delivery of nucleic acids *per se*. The desirability of this delivery is recognized universally. The methods can be used as research tools, delivery mechanisms for pharmaceuticals, and other applications as well as for "gene therapy."

With this background in mind, applicants point out that there is no criticism in the rejection that applicants have not taught a method successfully to introduce a nucleic acid molecule into a mammalian subject or to deliver a nucleic acid to a hair follicle or to deliver a nucleic acid to an intact tissue which is what applicants are claiming, not successful gene therapy. Accordingly, the rejection of claims 1-21 on this basis may be withdrawn.

The Rejections Under 35 U.S.C. § 102

Claims 10, 15, 17, 20 and 21 were rejected as assertedly anticipated by Li, *et al.* Claims 10, 20 and 21 have been canceled and the limitations of claims 16 and 18 have been incorporated into claims 15 and 17, respectively. Thus, this basis for rejection may be withdrawn.

Claims 11, 13, 17 and 20 were rejected as assertedly anticipated by either Poston, *et al.*, or Chapelier, *et al.* Claim 20 has been canceled. The limitations of claim 12 have been inserted into claim 11 from which claim 13 depends. The limitations of claim 18 have been inserted into claim 17. Accordingly, there is no longer basis for this rejection.

CONCLUSION

Claims 1-8, 11, 13-14, 15, 17 and 19 remain. The limitations of claim 12 have been inserted into claim 11, of claim 16 into claim 15 and of claim 18 into claim 17. Accordingly, all claims which now are pending have not been subject to any rejection over the art. Claim 9 has been canceled thus obviating the rejection for asserted lack of written description. It has been

shown that the remaining claims are directed not to gene therapy, but rather to methods to introduce a nucleic acid molecule either into a mammalian subject or into an intact histoculture tissue. The desirability of such improved methods is well understood and appreciated. There appears to be no basis to assert that applicants have not taught how to introduce nucleic acids into mammalian subjects or into intact tissues or hair follicles. Clearly the specification is enabling and provides a written description of such nucleic acid transfer. Whether aspects of "gene therapy" in the current state of the art warrant improvement is irrelevant to the invention as claimed. The invention claims only nucleic acid transfer, not gene therapy. Applicants therefore request that claims 1-8, 11, 13-15, 17 and 19 be passed to issue forthwith.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 312762002400.

Respectfully submitted,

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EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

11. (Amended) A method to introduce a nucleic acid molecule into a mammalian subject which method comprises transplanting into the corresponding tissue of said mammal a histocultured intact tissue that has been modified ex vivo to contain said nucleic acid molecule;

wherein said histoculture has been treated with collagenase prior to modifying said tissue with the nucleic acid.

15. (Amended) A method of delivering a nucleic acid to a hair follicle which method comprises maintaining said hair follicle in histoculture and treating said histoculture with a nucleic acid;

wherein said treating with a nucleic acid is preceded by the step of treating said histoculture with collagenase.

17. (Amended) A method of delivering a nucleic acid to a an intact tissue which method comprises treating a histoculture of said intact tissue with said nucleic acid;

wherein said treating with a nucleic acid is preceded by the step of treating said histoculture with collagenase.

19. (Amended) The method of claim [18] 17 wherein said tissue is skin or lymphoid.